Efficacy and acceptability of antidepressants

Take-home message:
Although there has been a lot of public debate about the role of antidepressants, a robust meta-analysis by Cipriani et al (1) has demonstrated that antidepressants are more effective than placebo in the treatment of Major Depressive Disorder.

Background
Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available. However, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, Cipriani et al (1) aimed to update and expand their previous work (2) to compare and rank the efficacy and acceptability of antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods
The analysis included a systematic review and network meta-analysis. It included double-blind, randomised controlled trials (RCTs) comparing antidepressants with placebo or another active antidepressant for the acute treatment of adults (≥18 years old and of both sexes) with a primary diagnosis of Major Depressive Disorder diagnosed according to standard operationalised diagnostic criteria. Only double-blind trials were considered, with quasi–randomised or incomplete trials, or trials which had at least 20% of patients with bipolar affective disorder/psychotic depression/treatment resistant depression or a serious concomitant medical illness excluded. Importantly the authors also sought unpublished trial data to avoid the issue of publication bias.

The analysis included 21 antidepressants approved by the regulatory agencies in the USA, Europe, or Japan. Overall, 522 double-blind, parallel, RCTs (including 116 477 patients) completed between 1979 and 2016 were included in the analysis. In total, 87 052 participants were randomly assigned to an active drug and 29 425 were randomly assigned to placebo. The mean age was 44 years (SD 9) for both men and women.

The great majority of patients had moderate to severe depression with a mean reported baseline severity score on the Hamilton Depression Rating Scale 17-item of 25·7 (SD 3·97). The included trials had outcomes recorded after a median of 8 weeks.

Primary outcomes were efficacy (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardised observer-rating scale for depression) and acceptability (treatment discontinuation measured by the proportion of patients who withdrew for any reason). Secondary outcomes were endpoint depression score, remission rate, and the proportion of patients who dropped out early because of adverse events.

Important findings

- **Efficacy**
    - All antidepressants were more effective than placebo, with odds ratios (ORs) ranging between 2·13 (95% credible interval [CrI] 1·89–2·41) for amitriptyline and 1·37 (1·16–1·63) for reboxetine compared to placebo.

    - In head to head comparisons of active drugs, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (ORs ranging between 1·19 and 1·96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were among the least efficacious drugs (ORs ranging between 0·51 and 0·84).

- **Acceptability**
    - Agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were better tolerated compared with other antidepressants (ORs for drop outs ranging between 0·43 and 0·77),

    - In head to head comparisons, amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine (ORs for drop outs: 1·30–2·32).

Comments

One limitation of the analysis was that the quality of many of the comparisons was moderate to low.

Dropout rates from RCTs is a potential poor proxy measure of acceptability of medication.

The analysis found few differences between antidepressants when all data (including placebo) were considered, while there was more diversity in the range of efficacy and dropout rates when just examining the more limited head-to-head comparisons.

Smaller and older studies presented larger effects of the active interventions versus placebo.

Great caution should be used in interpretation of the ranking of the various antidepressants, especially with regards to acceptability.

Summary

All antidepressants included in the study were more efficacious than placebo in adults with major depressive disorder. Differences in efficacy and tolerability were seen between the different antidepressants, though the relative rankings of antidepressants should be viewed with cuation.

Bibliography

1. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. Published online 21 February 2018. Doi: 10.1016/S0140-6736(17)32802-7.

2. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatment meta-analysis. *Lancet* 2009; 373: 746–58.

Authors

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